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White Matter Microstructural Abnormalities of the Cingulum Bundle in Youth with 22q11.2 Deletion Syndrome: Associations with Medication, Neuropsychological Function, and Prodromal Symptoms of Psychosis

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Abstract

Background—The 22q11.2 Deletion Syndrome (22q11.2DS) is regarded as an etiologically homogenous model for understanding neuroanatomic disruptions associated with a high risk for schizophrenia. This study utilized diffusion tensor imaging (DTI) to analyze white matter microstructure in individuals with 22q11.2DS. We focused on the cingulum bundle (CB), previously shown to be disrupted in patients with schizophrenia and associated with symptoms of psychosis.

Methods—White matter microstructure was assessed in the anterior, superior, and posterior CB using the tractography algorithm in DTIStudio. Neuropsychological function, presence of prodromal symptoms of psychosis, and medication history were assessed in all participants.

Results—Relative to controls, young adults with 22q11.2DS showed alterations in most DTI metrics of the CB. Alterations were associated with positive prodromal symptoms of psychosis. However, when individuals with 22q11.2DS were divided by usage of antipsychotics / mood stabilizers, the medicated and non-medicated groups differed significantly in axial diffusivity of

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Contributors WRK and ILC contributed to the conception and design of the study. MHG and PDR processed the data. MHG adapted the image processing protocol and implemented it along with JN. WRK analyzed the data. WRK, AO and ILC drafted the manuscript. ZK produced the scatterplots. All authors participated in the critical revision of the manuscript and provided final approval.

Conflicts of Interest The authors report no biomedical financial interests or potential conflicts of interest.

the anterior CB and in fractional anisotropy of the superior CB. DTI metrics did not differ between the medicated group and the control group.

Conclusions—Results suggest that the microstructure of the CB is altered in individuals with 22q11.2DS, and that those alterations may underlie positive prodromal symptoms of psychosis. Our findings further provide preliminary evidence that antipsychotic / mood stabilizer usage may have a reparative effect on white matter microstructure in prodromal 22q11.2DS, independent of the potential effects of psychosis. Future studies of white matter pathology in individuals with 22q11.2DS should test for potential effects of medication on white matter microstructure.

Keywords

Velo-cardio-facial Syndrome; Diffusion Tensor Imaging (DTI); cingulum bundle; prodromal symptoms of psychosis; schizophrenia; antipsychotics / mood stabilizers

1. Introduction

Chromosome 22q11.2 deletion syndrome (22q11.2DS; also known as velo-cardio-facial syndrome or DiGeorge syndrome) is a genetic neurodevelopmental disorder that occurs from an interstitial deletion of 40–50 genes on the long arm of chromosome 22. Individuals with 22q11.2DS often experience cardiac and craniofacial anomalies, as well as learning difficulties and emotional dysregulation (Simon et al., 2002; Swillen et al., 1997). Additionally, at least 25% of individuals with this syndrome go on to develop psychotic disorders, including schizophrenia, in young adulthood (Murphy et al., 1999), making 22q11.2DS the most common genetic basis for schizophrenia next to having two parents or a monozygotic twin with the disorder. Given the significant findings related to schizophrenia in 22q11.2DS, researchers have been exploring the links between the genetic defect, brain development, and the development of psychotic symptoms.

Early studies typically focused on grey matter changes, and most reported an overall significant reduction in total brain tissue and gray matter volumes in individuals with 22q11.2DS (Campbell et al., 2006; Dufour et al., 2008; Gothelf et al., 2011). Studies have also demonstrated white matter abnormalities, particularly volumetric deficits, in children (Campbell et al., 2006; Kates et al., 2001), adolescents (Baker et al., 2011), and adults (da Silva Alves et al., 2011; van Amelsvoort et al., 2001) with 22q11.2DS. A meta-analysis by Tan et al. (2009) concluded that 22q11.2DS is associated with global brain volumetric reduction affecting both gray and white matter, with specific cortical volumetric white matter reductions in temporal, parietal, and occipital lobe areas. Longitudinal studies have demonstrated that these volumetric white matter reductions persist into young adulthood (Gothelf et al., 2011; Gothelf et al., 2007).

Researchers have more recently begun to use diffusion tensor imaging (DTI) to examine white matter microstructure in individuals with 22q11.2DS. DTI allows us to probe the underlying microstructure of white matter anatomy by measuring the magnitude and direction of water diffusion in brain tissue in three dimensions. DTI provides several scalar parameters from which differences can be detected. The most commonly used parameter is fractional anisotropy (FA), which measures the extent to which diffusion is directionally

restricted. The FA level usually decreases in damaged white matter, but it remains unknown what type of damage has occurred (e.g., axon loss/membrane breakdown, demyelination, or gliosis/inflammation). Accordingly, other parameters obtained through DTI include radial diffusivity (RD), thought to be associated with the modulation of myelin in white matter, and axial diffusivity (AD), purportedly associated with axonal loss or disorganization (Budde et al., 2009; Song et al., 2002).

DTI studies in 22q11.2DS have shown abnormal white matter connectivity among individuals with 22q11.2DS, including reduced fractional anisotropy (FA) in interhemispheric connections, increased FA in frontal and parietal connections, and reduced FA in anterior-posterior projecting tracts (see Dennis and Thompson, 2013 for a review; Ottet et al., 2013). More specifically, Barnea-Goraly et al. (2003) reported decreased FA values in fronto-frontal and fronto-temporal tracts in individuals with 22q11.2DS. These areas also show aberrant connectivity in individuals with schizophrenia. Other significant DTI findings in 22q11.2DS include abnormalities within fibers of the visual ventral stream and a significant correlation between FA values in left parietal areas and arithmetic subtest scores (Barnea-Goraly et al., 2005; Kikinis et al., 2013). In addition, children with 22q11.2DS have higher parietal FA values that are related to poorer performance on an attentional counting task, thereby suggesting a different developmental trajectory related to disruption in parietal connectivity via the superior longitudinal fasciculus (SLF; Simon et al., 2008). Moreover, in an atlas-based study from our group, Radoeva et al. (2012) found significantly lower axial diffusivity (AD) in individuals with 22q11.2DS, including tracts terminating in parieto-occipital (posterior corona radiata), frontoparietal/occipital (inferior frontal occipital fasciculus [ILF], SLF), fronto-temporal, cingulum bundle (CB) and cerebellar areas, suggesting a widely distributed set of disrupted tracts in 22q11.2DS. Finally, Villalon-Reina et al. (2013) studied white matter tractography in 22q11.2DS, Turner Syndrome, and Fragile X Syndrome. Girls with 22q11.2DS showed more inferior longitudinal fasciculus (ILF) involvement in the right hemisphere, in more fronto-parietal areas, as opposed to the more temporo-parietal involvement seen in Turner Syndrome (Villalon-Reina et al., 2013). These findings provide a potential neuroanatomical background for the previously reported neuropsychological impairments in visuospatial ability, mathematics, and attention among children with 22q11.2DS (Antshel et al., 2006; Barnea-Goraly et al., 2005; Swillen et al., 1997).

Researchers have also investigated possible links between white matter tract integrity and psychiatric symptoms in 22q11.2DS. Sundram et al. (2010) reported a significant correlation between high schizotypy scores and decreased white matter FA in the right posterior limb of the internal capsule, and concluded that the microstructural abnormalities seen in individuals with 22q11.2DS may partially explain their schizotypic behaviors. Most recently, Perlstein et al. (2014) reported alterations in the anterior limb of the internal capsule (ALIC), fornix, and uncinate, and also observed associations between DTI metrics in ALIC and positive prodromal symptoms as measured by the Structured Interview for Prodromal Symptoms.

These studies, taken together, demonstrate the importance of studying white matter tract differences in helping to understand various neuropsychological and psychiatric impairments in individuals with 22q11.2DS. Although some studies speculate about the

underlying nature of the white matter tract integrity differences (i.e., axonal loss, myelination, or inflammation; (Kikinis et al., 2012; Radoeva et al., 2012), the use of FA in most studies leaves the exact cause of the differences unknown. In addition, most studies have included small sample sizes, and do not control for the potential effects of medication. Although results of DTI studies have not consistently shown a relationship between white matter volumes and medication (Kanaan et al., 2009; Kyriakopoulos et al., 2011), MRI research has demonstrated that antipsychotic medications – particularly atypical antipsychotics – may have a promyelinating effect. Specifically, their use has been associated with increased frontal white matter volume and intracortical myelin in individuals with schizophrenia (Bartzokis et al., 2009; Bartzokis et al., 2007). Accordingly, studies that incorporate potential effects of medications on white matter volumes and microstructure are warranted.

To date, few studies have examined the volume or white matter microstructure of the cingulate in individuals with 22q11.2DS. A volumetric study demonstrated bilateral volumetric reductions in cingulate gyrus cortical volume gray matter in 22q11.2DS compared to controls (Dufour et al., 2008). Furthermore, the authors observed a significant reduction in right cingulate gray matter volume in a low-performing executive functioning group (Dufour et al., 2008). As noted above, we have recently used a whole brain, atlas-based method to investigate white matter microstructure, and found that the anterior cingulum bundle (CB) (among other tracts) showed reductions in axial diffusivity (Radoeva et al., 2012). In a whole – brain voxel-based study of white matter, Simon et al. (2005) reported increased FA in a cluster of voxels that encompassed the anterior to posterior cingulate and splenium of the corpus callosum. Accordingly, studies that focus specifically on the white matter microstructure of the CB in 22q11.2DS are warranted, particularly since the cingulate is known to be disrupted in schizophrenia as well as associated with psychotic symptoms of the disorder (see Samartzis et al., 2014 for a review; Walterfang et al., 2011).

The cingulate has been a region of interest for neuroimaging studies of schizophrenia spectrum disorders due to its role in the processing of emotional stimuli, the expression of emotion, mood regulation, and executive functioning all of which are among the areas of impairment associated with the disorder (see Baiano et al., 2007 and Williamson and Allman, 2012 for reviews). DTI studies of individuals with schizophrenia have demonstrated decreased FA and increased diffusivity within prefrontal and temporal lobes, as well as abnormalities within fiber bundles connecting those regions, including the CB bundle (CB; Kubicki et al., 2007; Walterfang et al., 2011). More specifically, studies have shown a smaller mean area of and lower mean FA in the CB among individuals with schizophrenia (Kubicki et al., 2003), particularly the right anterior CB (Yan et al., 2012). Bilaterally decreased FA of both the dorsal and pregenual regions of the CB, have also been reported, as well as a significantly higher mean diffusivity (MD) in the bilateral dorsal area of the CB in individuals with schizophrenia (Takei et al., 2009). Associations between DTI scalars and executive function (Kubicki et al., 2003; Nestor et al., 2004), memory (Nestor et al., 2004) and cognitive control (Takei et al., 2009) in individuals with schizophrenia have also been reported.

Taken together, all of this evidence points to the importance of investigating white matter microstructure of the CB in individuals diagnosed with 22q11.2DS, including potential associations between DTI scalars and medication usage, neuropsychological function and prodromal symptoms of psychosis. Based on the extant literature noted above, the investigation that we report here was organized around the following hypotheses:

Hypothesis 1: Relative to the control sample, individuals with 22q11.2DS will demonstrate reduced FA, reduced AD and increased RD in the anterior and superior regions of the CB bundle (CB).

Hypothesis 2: Individuals with 22q11.2DS with a past or present history of antipsychotic medication or mood stabilizer usage will demonstrate increased FA and AD, and decreased RD relative to those without a history of such medication usage.

Hypothesis 3: In both controls and youth with 22q11.2DS, DTI scalar values will be associated with measures of executive function, verbal learning / working memory, and conflict monitoring.

Hypothesis 4: In youth with 22q11.2DS only, DTI scalar values will be associated with prodromal positive symptoms of psychosis.

2. Experimental/Materials and Methods

2.1. Participants

Here, we report on data collected on 97 participants, all of whom have been participating in a longitudinal study of risk for psychosis in 22q11.2 DS (Antshel et al., 2010; Antshel et al., 2008a; Antshel et al., 2008b; Antshel et al., 2007a; Antshel et al., 2007b; Antshel, et al., 2005a; Antshel et al., 2005b; Kates et al., 2011; Kates et al. 2007a; Kates et al. 2007b; Kates et al. 2006a; Kates et al. 2006b; Kates et al. 2005; Kates et al. 2004). Data from a subset of these participants (ie., 32 with 22q11.2DS; 16 controls) were also reported in an atlas-based, automated study of white matter microstructure (Radoeva et al., 2012) and in a tractography study of white matter microstructure (ie., 95 / 97 participants) (Perlstein et al., 2014). Study procedures were approved by the institutional review board of the SUNY Upstate Medical University, and all participants provided informed consent/assent. Participants were recruited from the Center for the Diagnosis, Treatment, and Study of Velo-Cardio-Facial Syndrome at SUNY Upstate Medical University and from the community. For the 22q11.2 DS participants, a microdeletion was confirmed by fluorescence *in situ* hybridization (FISH). All the details of this study, including exclusion criteria for all subjects are described in detail elsewhere (Kates et al., 2011).

This sample includes 51 participants with 22q11.2DS (22 male; mean age: 17.99, SD: 2.26; mean IQ: 73.2, SD: 13.87) and 46 age- and gender-matched controls (23 male; mean age: 18.05, SD: 1.59; mean IQ: 109.22, SD: 16.37) (Table 1). The control group included 21 unaffected siblings (9 male) and 25 community controls (14 male). Since siblings and community controls did not differ in any DTI metrics, we combined their data into one control sample. In the 22q11.2DS group, 11 participants (7 male) were treated with antipsychotic and mood stabilizing medication. A complete table with the medications that participants were taking at the time of their scan is in Table 1.

2.2. Neuropsychological Testing

The participants were assessed with a wide array of neuropsychological tests. Based on their age at the time of testing, the participants were either tested with Wechsler Adult Intelligence Scale, Third Edition (WAIS-III; Wechsler, 1997) or the Wechsler Intelligence Scale for Children— Third Edition (WISC-III; Wechsler, 1991). The *Wisconsin Card Sorting Test* (WCST; Heaton et al., 1993) was administered to assess executive function and concept formation. We used the Perseverative Error score for the current analyses. The *California Verbal Learning Test-Children's Version* (CVLT-C; Delis et al., 1994) was administered to test verbal learning and memory; List A was used in the current analyses. The *Stroop Color and Word Test* (Stroop; Golden, 1978) was utilized to assess the participants' cognitive flexibility and resistance to interference from outside stimuli. The color/word and the interference T-scores were utilized in our analyses.

2.3. Psychiatric Assessment

The Structured Interview for Prodromal Symptoms (SIPS; Miller et al., 2003) was administered by a doctoral-level child psychologist or psychiatrist. Inter-rater reliability, based on five SIPS interviews and assessed with the intra-class correlation coefficient, was 0.90. Since many of the children in our study had difficulty responding to a psychiatric interview, we reworded the Scale of Prodromal Symptoms (SOPS) questions to allow us to administer it to the child's parent as well as the child, and reduced the scale from a seven point to a five point Likert-type scale. Only the Positive Symptom Scale items were used for the present analyses.

2.4. Assessment of Medication History

Parents were asked to complete a medication history questionnaire on their child, in which we asked parents to list all of the current medications their child was taking, the reason for each medication, and age at which the child began each medication. We also asked for the same information about past medications that the child has begun taking since the last time point that we had seen them (generally three years prior to the current time point). Since age at which medication was started can be difficult to remember, we checked the medication information that the parent provided during the previous time point for consistency. Two discrepancies were noted, but they only differed by one year each (e.g. the parent stated in the current questionnaire that the child began a medication at age 8, and stated in the previous time point's questionnaire that the medication was started at age 9). These very few discrepancies support the overall reliability of this partially retrospective questionnaire.

2.5. Imaging Data Acquisition

The imaging data were acquired on a 1.5T Philips Interra scanner (release 11) equipped with a Sense Head coil to improve signal strength and signal-to-noise ratio. For DTI image acquisition, we utilized a multi-slice, single-shot EPI (SENSE factor = 2.0), spin echo sequence to acquire 70 axial slices, 2.5 mm nominal isotropic resolution (no gaps between slices) with the following scanning parameters: TR/TE = 8197/76 ms, FOV = 240 × 240, data matrix = 96 × 96, zero-filled and reconstructed to 256 × 256. Diffusion weighting was applied along 15 directions with a *b* factor=800 s/mm². One minimally weighted volume

(b_0) was acquired within each DTI dataset. The total scan time to acquire one DTI dataset (15 DW and 1 b_0 images) was 2 min, 11 s. Within the same scanning session, for each subject, we acquired four DTI datasets as well as a high-resolution T2W TSE scan to be utilized for re-alignment and co-registration purposes.

2.6. Diffusion Tensor Imaging Processing and Analysis

The imaging data was processed using DTIStudio 3.0.2 (<https://www.mristudio.org/>). By utilizing a mutual information algorithm, all diffusion weighted images from each DTI dataset were co-registered to the same reference volume, the b_0 volume of the first repeat (Woods et al. 1993). Axial slices with severe scanning and motion artifacts were excluded via automatic outlier slice rejection in DTIStudio (with relative error > 3%), and through visual inspection. Following the slice exclusion, tensor estimation was performed. The high-resolution T2 scan of each participant was reoriented in anterior commissure – posterior commissure space. Then the B_0 (along with its corresponding tensor file) was realigned using a linear registration transformation to the high-resolution T2 scan. FA, AD, and RD maps were then generated based on the tensor file in AC-PC space.

One-tensor streamline tractography (FACT fibertracking) reconstruction was performed to identify the anterior, superior, and the posterior parts of the CB (see Supplementary Figure 1) following a protocol derived from (Concha et al., 2005). Seeding was started on all voxels within the seeding ROI with an FA value greater than 0.3; tractography was stopped in locations where the FA value was less than 0.3 or if the tract turning angle was above 70. We were unable to reconstruct any parts of the CB for one individual with 22q11.2DS and therefore excluded that participant from the sample described above. In the left hemisphere, the anterior subregion was not reconstructed for 4 individuals (3 with 22q11.2DS and 1 control), the superior subregion for one control individual, and the posterior subregion for one 22q11.2DS individual. In the right hemisphere, the anterior subregion for 3 individuals (1 with 22q11.2DS and 2 controls), and the superior subregion for one control individual were not reconstructed. Inter-rater reliability for all subregions of the CB, based on 10 subjects by two raters, and calculated with the intraclass correlation coefficient (ICC), was high, ranging between 0.96 and 0.99.

2.7. Statistical Analysis

Multivariate analyses of variance (MANOVAs) were conducted to compare DTI metrics (i.e., left and right FA, AD and RD) for each CB subregion between study groups. MANOVAs were first conducted with study group consisting of the control sample and the total 22q11.2DS sample. A second set of MANOVAs was conducted with study group consisting of the control sample and two subgroups of participants with 22q11.2DS: one group with a current / past history of antipsychotic or mood stabilizer use, and a group without such a history. Then, three – group MANCOVAs were conducted that covaried for age, full scale IQ, and SOPS-Positive Symptoms scores. Pearson r correlations were conducted, separately for each total study group, to test the association between DTI metrics and neuropsychological variables. Associations between DTI metrics and the SOPS were assessed with the Zero-Inflated Poisson (ZIP) regression analyses (Lambert, 1992), since the

distribution of our SOPS data included at least 50% of scores equaling zero (indicating the absence of positive prodromal symptoms).

3. Results

3.1. Hypothesis 1: Study Group Differences

Relative to the combined group of siblings and controls, participants with 22q11.2DS demonstrated significant alterations in the three subregions of the CB (See Supplementary Table 1; Supplementary Figure 2). Individuals with 22q11.2DS demonstrated reductions in left FA, and left and right AD in the anterior CB; reductions in left and right AD, and right RD in the superior CB; and increases in left and right FA, and decreases in left and right RD in the posterior CB.

3.2. Hypothesis 2: Effects of Medication

When the group of participants with 22q11.2DS was divided into those with and without a current or past history of antipsychotics (A) or mood stabilizers (MS), those without a history of A/MS (22q11.2DS – A/MS) continued to demonstrate anterior CB reductions in left FA, and left and right AD, relative to controls (see Table 2, Figure 1). Interestingly, however, no significant differences were found between participants with a history of A/MS (22q11.2DS + A/MS) and controls for left FA or left and right AD. Moreover, relative to 22q11.2DS – A/MS, right AD was significantly higher in 22q11.2DS + A/MS. Similarly in the superior CB, right FA was significantly lower in 22q11.2DS – A/MS relative to controls, but 22q11.2DS + A/MS did not differ from controls. Moreover, right FA was significantly higher in 22q11.2DS + A/MS relative to 22q11.2DS – A/MS. To summarize, the medicated and the non-medicated 22q11.2DS participants show statistically significant differences in AD in the left anterior CB and in FA in the left superior CB, and, interestingly, the medicated group has the same values of DTI measures as the control group (Figure 1). Medication status did not alter results in the posterior CB.

In an effort to determine the extent to which other variables could account for the differences in DTI metrics between 22q11.2DS + A/MS and 22q11.2DS – A/MS, we ran the three-group MANCOVAs with covariates, entering age, FSIQ and SOPS-Positive Symptom scores in separate analyses. All of the overall multivariate models (i.e., Wilks' Lambda values) remained significant. Planned, follow-up comparisons between the 22q11.2DS + A/MS and 22q11.2DS – A/MS groups indicated that left AD of anterior CB remained significantly higher in 22q11.2DS + A/MS group, even when covarying for age, FSIQ or SOPS-Positive Symptom scores. Left FA of the superior CB remained significantly higher in 22q11.2DS + A/MS group when FSIQ or SOPS-Positive Symptom scores were added as covariates. When age was entered into the model, significance dropped to trend level ($p = .08$), possibly due to the fact that the 22q11.2DS + A/MS group is slightly, but not significantly, older than the 22q11.2DS – A/MS group. Follow-up comparisons between the controls and the 22q11.2DS – A/MS groups indicated that the addition of covariates of age or SOPS – Positive Symptom scores did not alter the significance of the results.

3.3. Hypothesis 3: Association with Neuropsychological Functioning

After applying the Benjamini-Hochberg false discovery rate (FDR) correction for multiple comparisons, we found that in the combined control sample, perseverative error scores on the Wisconsin Card Sorting Task were significantly associated with DTI metrics, such that fewer perseverative errors were associated with higher FA of the left anterior CB ($r = .54$; $p = .0001$; FDR - adjusted $p = .004$) and higher FA of the right superior CB ($r = .523$; $p = .0001$; FDR - adjusted $p = .004$). Scores were not associated with DTI indices in the group of participants with 22q11.2DS. Further in the control sample, scores on the CVLT were significantly associated with DTI metrics, such that higher scores for List A of the CVLT were associated with higher FA of the left superior CB ($r = .504$; $p = .0001$; FDR - adjusted $p = .04$). CVLT List A scores were not significantly associated with DTI indices for the participants with 22q11.2DS. Scores on the Stroop were not significantly associated with DTI indices for either study group.

3.4. Hypothesis 4: Association with Positive Symptoms of Psychosis

After correcting for multiple comparisons, we found that within the group of participants with 22q11.2DS, higher SOPS-Positive Symptom scores were associated with higher left ($z = 2.55$; $p = .011$; FDR - adjusted $p = .0495$) and right ($z = 4.20$; $p = .0001$; FDR - adjusted $p = .0018$) FA, and lower left ($z = -3.29$; $p = .001$; FDR - adjusted $p = .009$) and right ($z = -2.88$; $p = .004$; FDR - adjusted $p = .024$) RD of the superior CB (see Figure 2).

4. Discussion

This is the first study, to our knowledge, to report alterations in the CB in individuals diagnosed with 22q11.2DS based on manual tractography methods. Structural (Dufour et al., 2008) reductions of the volume of the cingulate gyrus in 22q11.2DS have been reported previously. Moreover an automated, atlas-based study of white matter microstructure applied by our group (to a subset of the current sample) has found reductions in AD in the region of the cingulated gyrus that corresponded to the anterior, and a portion of the superior, CB in the current report. Accordingly, the current findings extend that study by increasing the sample size and by applying manual tractography, thus permitting a more specific interrogation of the subregions of the cingulate that may be affected in individuals with this syndrome.

Consistent with our previous atlas-based report, the most robust differences that we found between participants with 22q11.2DS and controls were in axial diffusivity, which was reduced significantly in the anterior (as was left FA) and superior segments of the CB in participants with 22q11.2DS, suggesting axonal damage or disorganization (Budde et al., 2009; Song et al., 2003). Neuropathological (Kiehl et al., 2009) and animal (Meehan et al., 2009) studies suggest that 22q11.2DS is a disorder of early neuronal migration. It has been demonstrated that neuronal migration may influence axonal placement via its mediation of axonal guidance cues (Lopez-Bendito et al., 2006), suggesting that white matter microstructural anomalies may be due to early neurodevelopmental disruptions. However, it has also been shown that AD (and FA) increase during adolescence in typical youth (Kubicki et al., 2013; Kumar et al., 2013; Wu et al., 2014) suggesting that axonal coherence

continues to improve during adolescence. Interestingly, in the case of 22q11.2DS improvement to normal levels might not be reached, as a DTI study of adults with 22q11.2DS found that FA and AD remain reduced (Kikinis et al., 2013; Kikinis et al., 2012). This implies that white matter pathology in 22q11.2DS may involve both early aberrant developmental and ongoing deleterious processes. This latter notion is also supported by our finding that right RD was also significantly altered in the superior CB, as well as in the posterior CB of participants with 22q11.2DS. RD has been associated with myelin integrity (Song et al., 2005), which continues to develop into the third decade of life (Benes et al., 1994).

Although several cytoarchitectonically distinct subregions of the cingulate have been identified, CB circuitry in general consists of reciprocal, fronto-temporal connections, linking the cingulate to lateral prefrontal and orbitofrontal cortices, superior temporal gyrus, entorhinal cortex, and hippocampus (Dum and Strick, 1993; Van Hoesen et al., 1993; Vogt et al., 1992). As such, it represents a primary circuit of the limbic system. Functional studies indicate that the cingulate is involved in attention, error detection (Bush, 2011), response inhibition (Bush et al., 2003); executive function (Carter et al., 2001; Morey et al., 2005) and emotion modulation (Allman et al., 2001; Mega et al., 1997).

Accordingly, we examined associations between DTI indices and neuropsychological measures of executive function, verbal learning/working memory, and conflict monitoring. We found that DTI indices of the anterior and superior CB were significantly associated with executive function and verbal learning/working memory skills in typical youth. Despite functional imaging studies that have reported impairments in cingulate activation during tasks of working memory (Kates et al., 2007), however, in youth with 22q11.2DS, we did not find the expected association with behavioral tests of executive function or verbal learning/working memory in our participants with 22q11.2DS. It is possible that the complexity of the disorder may be affecting direct associations between brain and behavior: that is, gene dosage effects may be influencing the neuroanatomical phenotype, and the presence of psychosis may be altering neuropsychological phenotype in ways that alter expected associations.

Contrary to our lack of significant associations between neuropsychological functioning and DTI indices of the CB in our 22q11.2DS cohort, we found associations between the SOPS Positive Symptoms scores and DTI metrics throughout the CB. The direction of most of the associations was counter-intuitive (positive associations between FA, and negative associations between RD, and SOPS scores), although these findings are consistent with our recently reported finding of increased FA of the anterior limb of the internal capsule with SOPS-PS scores (Perlstein et al., 2014). Although most studies have found a negative association between FA and symptoms of psychosis, a positive association between FA and degree of hallucinations has also been reported (Alba-Ferrara and de Erausquin, 2013; Rotarska-Jagiela et al., 2009; Shergill et al., 2007; Whitford et al., 2010), including in the CB (Hubl et al., 2004). It has been hypothesized (Alba-Ferrara and de Erausquin, 2013) that deficient axonal pruning in schizophrenia may be associated with decreased efficiency in the transmission of information, which is then reflected in increased FA in individuals with

schizophrenia. Studies using animal models would be useful in testing the associations between axonal pruning, information transmission, and FA more directly.

We further found an association between medication status and DTI metrics, such that our findings of reduced FA and AD in participants with 22q11.2DS relative to controls did not hold up for the subgroup of patients with 22q11.2DS who had a present or past history of antipsychotic or mood stabilizer use. Moreover, we found that left FA of the superior CB and left AD of the anterior CB was significantly higher in the 22q11.2DS participants with a history of such medication usage relative to those without. These differences did not appear to be due to variance in IQ or (in the case of the anterior CB) age, and importantly, held up when the presence of positive symptoms of psychosis were included in the model.

Accordingly, our findings provide preliminary evidence that history of antipsychotic / mood stabilizer usage may have a reparative effect on white matter microstructure independent of the potential effects of psychosis. Although very few studies have found an association between medication status and DTI signal specifically, associations between antipsychotic medication and changes in white matter have been inconsistently noted in both animal models and human studies. In murine models, antipsychotic medication has been shown to play a role in the differentiation (Fang et al., 2013) and regeneration (Xiao et al., 2008; Zhang et al., 2008) of oligodendrocytes and myelin repair in myelin-deficient murine models, whereas in primates, antipsychotic-exposed animals had non-significantly lower numbers of oligodendrocytes (Konopaske et al., 2008) relative to non-exposed animals. In humans, it has been reported that antipsychotic dosage is associated with increased FA (Minami et al., 2003) and increased volumes of white matter (Bartzokis et al., 2007) in frontal lobe. Interestingly, although Ho and colleagues (2011) found that higher doses of typical antipsychotics and non-clozapine atypical antipsychotics were associated with smaller gray matter volumes, they were associated with larger parietal white matter volumes. However, other studies have reported either decreases in, or no effects on, white matter volumes as a result of antipsychotic usage (Andreasen et al., 2013; Kanaan et al., 2009; Peters et al., 2008; Szeszko et al., 2014). For example, a recent meta-analysis (Fusar-Poli et al., 2013) of 30 studies, involving 1046 individuals with schizophrenia and 780 controls, found that longitudinal decreases in gray matter volumes were associated with higher exposure to antipsychotics over time. Inconsistency in findings may be due, in part, to the class (atypical vs. typical antipsychotics; Bartzokis et al., 2007), timing and dosage of the administration of the medication (Walterfang et al., 2011), and additional studies are clearly warranted. Our findings demonstrate the importance of testing for the potential effects of medication in studies of white matter microstructure in individuals with 22q11.2DS.

Potential limitations to our study should be considered. Our DTI acquisition was on a 1.5 Tesla scanner, which may have limited image resolution and performance of our fiber tracking algorithms, as possibly evidenced by the cases for which we could not reconstruct aspects of the CB. In addition, our interpretation of the potential effects of medication usage is limited by the small number of participants exposed to antipsychotics / mood stabilizers, the partially retrospective nature of our medication questionnaire, and by the absence of information about specific dosages or length of medication use. Moreover, it should be noted that youth with 22q11.2DS are often prescribed antipsychotics and mood stabilizers

several years prior to the onset of psychosis; accordingly, it is critical that this association be investigated in a future, longitudinal study that begins when the youth are in middle childhood, and that image acquisitions be repeated at multiple timepoints throughout adolescence. Multi-site studies that can ensure large samples of youth with 22q11.2DS will be required to implement such a design.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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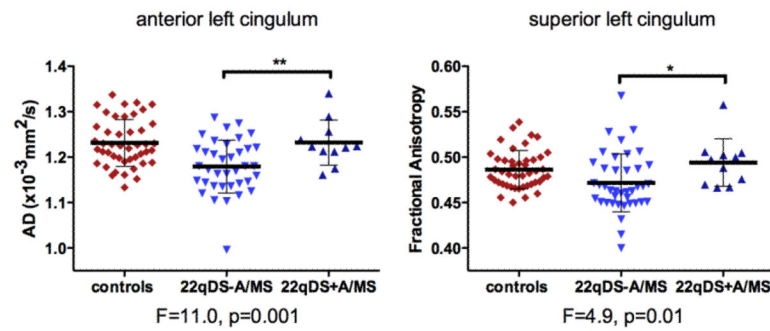


Figure 1.

These scatterplots depict the distribution of data points for the DTI metrics for which the subgroup of youth with 22q11.2DS and a current / past history of antipsychotic medication / mood stabilizers (22qDS+A/MS) differed significantly from the subgroup of youth with 22q11.2DS without such a history (22qDS-A/MS). Bars represent means and standard deviations.

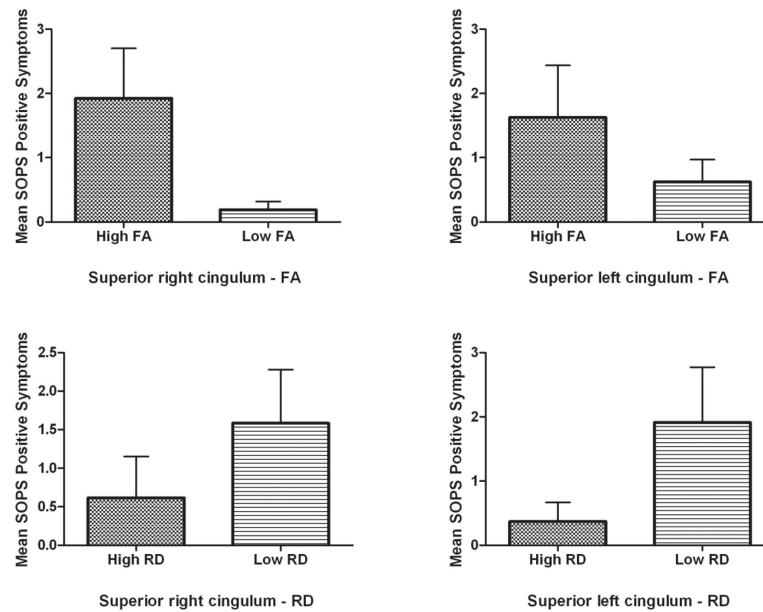


Figure 2.

These bar graphs depict significant associations between Scale of Prodromal Symptoms (SOPS) Positive Symptoms scores and DTI metrics in youth with 22q11.2DS, after correcting for multiple comparisons. Following a median split of each significant DTI metric, participants were assigned to either a High group or a Low group, and the mean SOPS Positive Symptom score was plotted for each group.

Table 1

Demographic Characteristics of Participants (N = 97)

Characteristic	22q11.2DS (<i>n</i> = 51)	Controls (<i>n</i> = 46)	<i>p</i> -value
Gender (n, % male)	22 (56.8)	23 (50)	ns
Age in years (+/- SD)	18 (2.3)	18 (1.6)	ns
Range	14 – 24	15 – 21	
Full Scale IQ (+/- SD)	73 (13.9)	109 (16.4)	< .001
Range	40 – 98	68 – 153	
Medication *			
Antipsychotic (current and/or past)	7 (13.73%)	0	
Mood Stabilizer (current and/or past)	6 (11.76%)	0	
Anti-depressant/anxiety (current)	7 (13.73%)	3 (6.52%)	
Stimulant/Alpha 2 Adrenergic (current)	11 (21.57%)	5 (10.87%)	
No medication	32 (62.7%)	39 (84.8%)	

* Several participants are on multiple medication regimens that cross multiple medication classes.

Table 2

Group Differences in Fractional Anisotropy, Axial Diffusivity, and Radial Diffusivity of Cingulum Areas Based on Medication Status

	Controls (n = 43)	22q-A/MS (n = 36)	22q+A/MS (n = 11)	F	p	η^2	Main Effects
Anterior Cingulum ^a							
FA							
Left	0.459 ± 0.027	0.442 ± 0.028	0.456 ± 0.029	3.813	.026	.08	C>22q-A/MS; C=22q+A/MS; 22q+A/MS=22q-A/MS
Right	0.397 ± 0.028	0.386 ± 0.031	0.405 ± 0.036	2.245	.112	.049	
AD							
Left	0.00123 ± 5.3×10 ⁻⁵	0.00119 ± 6.1×10 ⁻⁵	0.00123 ± 5.0×10 ⁻⁵	10.991	.001	.201	C>22q-A/MS; C=22q+A/MS; 22q+A/MS>22q-A/MS
Right	0.00123 ± 5.3×10 ⁻⁵	0.00119 ± 5.4×10 ⁻⁵	0.00121 ± 5.0×10 ⁻⁵	6.531	.002	.131	C>22q-A/MS; C=22q+A/MS; 22q+A/MS<22q-A/MS
RD							
Left	5.8×10 ⁻⁴ ± 3.3×10 ⁻⁵	5.8×10 ⁻⁴ ± 4.9×10 ⁻⁵	5.7×10 ⁻⁴ ± 4.0×10 ⁻⁵	0.622	.539	.014	
Right	6.4×10 ⁻⁴ ± 3.9×10 ⁻⁵	6.4×10 ⁻⁴ ± 4.1×10 ⁻⁵	6.4×10 ⁻⁴ ± 3.9×10 ⁻⁵	0.303	.739	.007	
Superior Cingulum ^b							
FA							
Left	0.487 ± 0.022	0.472 ± 0.032	0.494 ± .026	4.877	.010	.096	C>22q-A/MS; C=22q+A/MS; 22q+A/MS>22q-A/MS
Right	0.462 ± 0.022	0.455 ± 0.028	0.471 ± .024	1.944	.149	.041	
AD							
Left	0.00131 ± 6.4×10 ⁻⁵	0.00124 ± 5.2×10 ⁻⁵	0.00126 ± 3.6×10 ⁻⁵	16.608	.0001	.265	C>22q-A/MS; C=22q+A/MS; 22q+A/MS=22q-A/MS
Right	0.00131 ± 6.3×10 ⁻⁵	0.00125 ± 4.9×10 ⁻⁵	0.00125 ± 4.8×10 ⁻⁵	18.584	.0001	.288	C>22q-A/MS; C=22q+A/MS; 22q+A/MS=22q-A/MS
RD							
Left	5.7×10 ⁻⁴ ± 3.7×10 ⁻⁵	5.6×10 ⁻⁴ ± 4.8×10 ⁻⁵	5.4×10 ⁻⁴ ± 4.3×10 ⁻⁵	2.775	.068	.041	
Right	6.0×10 ⁻⁴ ± 3.5×10 ⁻⁵	5.8×10 ⁻⁴ ± 3.5×10 ⁻⁵	5.9×10 ⁻⁴ ± 3.7×10 ⁻⁵	6.009	.004	.116	C>22q-A/MS; C=22q+A/MS; 22q+A/MS=22q-A/MS
Posterior Cingulum ^c							
FA							
Left	0.424 ± 0.022	0.437 ± 0.030	0.446 ± .028	3.946	.023	.078	
Right	0.419 ± 0.026	0.439 ± 0.027	0.434 ± .024	6.204	.003	.118	C<22q-A/MS; C=22q+A/MS; 22q+A/MS=22q-A/MS
AD							
Left	0.00125 ± 6.0×10 ⁻⁵	0.00125 ± 6.8×10 ⁻⁵	0.00125 ± 6.1×10 ⁻⁵	.091	.913	.002	
Right	0.00126 ± 5.3×10 ⁻⁵	0.00126 ± 4.5×10 ⁻⁵	0.00127 ± 5.0×10 ⁻⁵	.259	.772	.006	

	Controls	22q-A/MS	22q+A/MS	F	p	η ²	Main Effects
RD							
Left	6.2×10 ⁻⁴ ± 4.2×10 ⁻⁵	6.0×10 ⁻⁴ ± 4.8×10 ⁻⁵	6.0×10 ⁻⁴ ± 2.6×10 ⁻⁵	2.146	.123	.044	
Right	6.2×10 ⁻⁴ ± 3.9×10 ⁻⁵	6.0×10 ⁻⁴ ± 4.3×10 ⁻⁵	6.1×10 ⁻⁴ ± 4.1×10 ⁻⁵	2.408	.096	.049	

Note. FA = Fractional Anisotropy; AD = Axial Diffusivity; RD = Radial Diffusivity; C = Controls; 22q-A/MS = Participants with 22q without past or present usage of antipsychotics or mood stabilizers; 22q+A/MS = Participants with 22q with past or present usage of antipsychotics or mood stabilizers.

^aWilks' Lambda: .69; *F* [6, 82] = 2.80; *p* = .002; η² = .230

^bWilks' Lambda: .59; *F* [6, 87] = 4.32; *p* = .0001; η² = .366

^cWilks' Lambda: .78; *F* [6, 88] = 2.75; *p* = .031; η² = .118